**Statins and Blood Coagulation**

Anetta Undas, Kathleen E. Brummel-Ziedins, Kenneth G. Mann

**Abstract**—The 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors (statins) have been shown to exhibit several vascular protective effects, including antithrombotic properties, that are not related to changes in lipid profile. There is growing evidence that treatment with statins can lead to a significant downregulation of the blood coagulation cascade, most probably as a result of decreased tissue factor expression, which leads to reduced thrombin generation. Accordingly, statin use has been associated with impairment of several coagulant reactions catalyzed by this enzyme. Moreover, evidence indicates that statins, via increased thrombomodulin expression on endothelial cells, may enhance the activity of the protein C anticoagulant pathway. Most of the antithrombotic effects of statins are attributed to the inhibition of isoprenylation of signaling proteins. These novel properties of statins, suggesting that these drugs might act as mild anticoagulants, may explain, at least in part, the therapeutic benefits observed in a wide spectrum of patients with varying cholesterol levels, including subjects with acute coronary events. *(Arterioscler Thromb Vasc Biol. 2005;25:287-294.)*

**Key Words:** statins ■ blood coagulation ■ thrombin ■ protein C

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, the so-called statins, have been proven to be highly effective in the management of hyperlipidemia and the prevention of atherosclerotic vascular disease, especially coronary artery disease (CAD). The therapeutic benefits from statin therapy, however, are only poorly correlated with cholesterol lowering, suggesting other mechanisms are at play. Mevalonate, the product of HMG-CoA reductase, is the precursor of not only cholesterol but also isoprenoid compounds that permit the attachment of signaling proteins to the cell membrane.

Abundant experimental and clinical evidence in this rapidly expanding field has resulted in the widely accepted concept of cholesterol-independent pleiotropic effects produced by statins that include alteration of endothelial dysfunction, leading to increased nitric oxide (NO) bioavailability, atherosclerotic plaque stabilization, regulation of angiogenesis, reduction of the inflammatory response, and antithrombotic properties. Apart from profibrinolytic and antiplatelet effects, reported in several studies, increasing evidence indicates that the HMG-CoA reductase inhibitors also modulate the blood coagulation cascade at multiple levels, leading to reduced thrombogenicity.

The activation of the extrinsic coagulation pathway initiated by an exposure or expression of tissue factor (TF) plays a key role in hemostasis (Figure). The localized process involves multiple components, including blood coagulation factors, platelets, blood cells, the endothelium, and sublayers of a damaged vessel. Platelets provide the catalytic surface for the formation of the procoagulant complexes; the intrinsic factor Xase (FIXa-FVIIIa) and prothrombinase (prothrombin, FXa-FVa). These complexes accelerate thrombin generation by many orders of magnitude.

The TF-initiated blood coagulation process contributes to the formation of fibrin-rich clots not only in the veins but also in platelet-rich thrombi typical of the high-flow, high-pressure arterial system in which thrombosis develops usually on a ruptured atheromatous lesion. Thus, attenuation of TF-induced blood coagulation has broad clinical implications. In this review, we summarize the available data on effects of different HMG-CoA reductase inhibitors on blood clotting and outline potential clinical implications of these properties in the thrombotic manifestations of vascular disease.

**Initiation**

TF, the transmembrane glycoprotein, is the principal physiological initiator of blood clotting by serving as the cofactor for activated FVII (FVIIa). The latter is an inactive enzyme, unless bound to TF. Colli et al demonstrated that simvastatin and fluvastatin, used at concentrations close to peak serum values observed in humans, but not pravastatin at concentrations 100 times greater than those found effective for lipophilic statins, decrease TF mRNA expression and activity in cultured human monocytes/macrophages obtained from healthy individuals. This dose-dependent effect observed from lipopolysaccharides (LPS) (unstimulated and...
stimulated cells) was reversed by coinubcation with mevalonate or geranangerlyl pyrophosphate, but not by cholesterol.

A decrease in TF expression has been found to be, in part, mediated by the inhibition of the activation of a transcription nuclear factor κB (NF-κB).13 Hilgendorff et al,14 however, have shown that cerivastatin, atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin, in this order, can reduce NF-κB activation, from 45% inhibition for cerivastatin to 5% for fluvastatin, in human monocytes incubated with LPS. Importantly, these differences in the potency of HMG-CoA reductase inhibitors resulted in different TF expression.14 A significant reduction in TF expression after a 6-hour incubation with simvastatin (0.01 to 10 μmol/L) has also been shown in human LPS-stimulated monocytes isolated from hypercholesterolemic subjects.15 Moreover, Ferro et al15 demonstrated the inhibition of thrombin generation by simvastatin in a dose-dependent manner in their in vitro model. Simvastatin in the range of 100 nmol/L to 1 μmol/L has also been reported to inhibit thrombin-induced TF expression in human aortic endothelial cells, and this effect has been associated with reduced RhoA kinase activation.16 Nagata et al17 have found that not only cerivastatin but also pravastatin are able to reduce the levels of TF antigen and mRNA via the inhibition of geranangerlylation of Rho in cultured human monocytes, which suggests that decreased TF expression is likely a class effect of the HMG-CoA reductase inhibitors. In addition, this study supported the view that inhibition of Rho/β-kinase signaling, involved in the monocyte synthesis of TF, largely contributes to decrease in TF expression induced by statins.

Favorable modulation of TF expression in the arteries has been documented in animal models, such as cynomolgus monkeys on atherogenic diet,18 Watanabe Heritable Hyperlipidemic (WHHL) rabbits, a model of isolated hypercholesterolemia,19 apolipoprotein E-deficient mice,20 and in cholesterol-fed rabbits.21 Treatment with cerivastatin,19 simvastatin,18,20 pravastatin,18 and fluvastatin21 substantially reduced TF expression in atherosclerotic lesions, along with suppression of inflammation in atheroma, independently of lipid lowering.18,20,21 These findings have been corroborated in humans by the findings of the double-blind, placebo-controlled ATROCAP (the Atorvastatin and Thrombogenic- Arterioscler Thromb Vasc Biol. February 2005

Factor VII

Activated FVII in complex with TF activates FX in the surface-bound extrinsic factor tenase complex, and via activation of FIX contributes to the formation of the intrinsic factor tenase, which is 50-fold more efficient in FX activation than the extrinsic tenase.10–12 A concept of statin-induced changes in FVIIa activity and levels has attracted much interest, although reliable assays for determination of 2-chain FVIIa have not been developed until recent years, which hampered the interpretation of published reports. In hypercholesterolemic patients, factor VII antigen levels and FVII coagulant activity in commercially available clot-based assays have been reported to be slightly (<12%), but significantly, lower during a 12-week treatment with atorvastatin (10 mg/d)23 and 4 to 6 weeks of atorvastatin use at a dose of 20 mg daily.24 Both changes were unrelated to cholesterol lowering by this agent. However, FVIIa activity, determined with a 1-stage clotting assay using a recombinant truncated TF as a specific cofactor, remained unaltered after such therapy,23 suggesting that even if the drug lowers FVII production, which has not been shown in vitro so far, the activity of an active form of FVII is not affected by the inhibition of HMG-CoA reductase in vivo. Higher doses, for example, atorvastatin 80 mg/d, seem not to be more effective because this statin, administered for 12 weeks in hyperlipidemic subjects, also reduced FVII coagulant activity by 8%.25 However, there have been reports demonstrating that simvastatin,26 pravastatin,27 and fluvastatin28 have no effect on FVII levels and/or coagulant activity. Further studies using specific assays to quantify FVIIa levels in the circulating blood are needed to explain whether statins can modulate the activity of the initiator complex TF–FVIIa via not only TF expression but also FVIIa formation and/or activity.

Thrombin Formation and Thrombin-Mediated Coagulant Reactions

Thrombin

Thrombin, a multifunctional serine protease, orchestrates blood clotting in vivo.10,11 A body of evidence accumulating throughout the past decade, derived from a variety of in vitro and in vivo studies, indicates that statin therapy results in decreased thrombin formation.5–9 Methodological approaches to the evaluation of the effect of HMG-CoA reductase inhibitors on thrombin formation encompass: (1) measurements of thrombin markers in venous blood drawn from treated subjects; (2) ex vivo perfusion systems that evaluate thrombotic potential of the blood obtained from these patients and exposed to thrombogenic substrate at various flow velocities;27,29,30 (3) in vitro models of thrombin formation in recalcified plasma;31 and (4) analysis of prothrombin activation, performed in consecutive blood samples collected from standardized bleeding-time wounds (the Simplate model).32,33

Significant reductions in thrombin generation, reflected by lower levels of prothrombin fragment F1.2 (residues 1 to 156) cleaved from the prothrombin molecule by thrombin, were observed in hypercholesterolemic subjects.34–36 A significant decrease in plasma thrombin marker levels at 3 months of treatment with atorvastatin, simvastatin, or pravastatin was also demonstrated in peripheral venous blood.34 However, some data seemed to suggest that pravastatin might be deprived of thrombin-lowering ability.34 As early as in 1995, Lacoste et al30 demonstrated a significant reduction of mural thrombus formation on porcine aortic media exposed to the flowing blood assessed in 16 patients with previous myocardial infarction and elevated cholesterol levels that used pravastatin 40 mg/d. This finding clearly indicated that
correction of increased thrombogenic potential might be important in clinical benefits observed within the first few months after an acute coronary event. In the perfusion chamber mimicking mild stenosis of the artery, Dangas et al observed a significant decrease (34%) in the thrombus area in hypercholesterolemic subjects without signs of CAD and only a 16% decrease in CAD patients after 6 months of pravastatin use. These reductions were modestly correlated with the magnitude of changes in low-density lipoprotein (LDL) cholesterol.

The blood coagulation cascade and proteins or reactions reportedly affected by statin therapy. There are 2 pathways to initiate coagulation, the contact intrinsic pathway (shown in the center) and the primary extrinsic pathway (shown on the right). These multicomponent processes are illustrated as enzymes (circles), inhibitors (hatched circles), zymogens (boxes), or complexes (ovals). Fibrin formation is also shown (oval). Statins effect on the proteins or pathways are shown in color (red indicates statin decrease the effect; blue, statin increases the effect). The contact pathway has no known bleeding cause associated with it, thus this path is considered accessory to hemostasis. On injury to the vessel wall, tissue factor, the cofactor for the extrinsic tenase complex, is exposed to circulating factor VIIa and forms the vitamin K-dependent complex the extrinsic tenase. Factor IX and factor X are converted to their serine proteases factor IXa (FIXa) and factor Xa (FXa), which then form the procoagulant complex the extrinsic tenase. Factor IX is activated through procoagulant mechanisms, thrombin cleaves fibrinogen (releasing fibrinopeptide A and B [FPA and FPB]) and activate factor XIII to form a cross-linked fibrin clot. Thrombin–thrombomodulin also activates thrombin–thrombomodulin inhibitors that slows fibrinogen activation under dynamic flow conditions that were augmented before the initiation of hypolipidemic therapy, and the reduction in blood thrombogenicity was not related to changes in cholesterol levels. Also in recalcified plasma, pravastatin 15 mg/d has been effective in reducing platelet-dependent thrombin generation in hypercholesterolemic subjects. Using a model of microvascular injury, which reflects TF-initiated blood coagulation, we have demonstrated that simvastatin 20 to 40 mg/d depresses thrombin generation in subjects with hypercholesterolemia. We found that at the site of hemostatic plug formation, depletion of prothrombin was reduced by 16%, whereas the rate of formation of prothrombin activation products, such as F1.2, prethrombin 2 (residues 274 to 579), and thrombin B-chain, was decreased by 27% and the time of their appearance was delayed by ~60 seconds in hypercholesterolemic subjects receiving simvastatin.

Unlike studies performed in stable patients, there are little available data regarding statin-induced effects on initially markedly elevated blood thrombogenicity in acute coronary
syndromes (ACS), and these studies have not provided evidence for the presence of thrombin-lowering action of statins in this clinical setting. Olivotti et al did not observe reduction in plasma F1.2 levels or thrombin formation in thrombi formed in vitro among patients with ACS treated with high-dose atorvastatin for 16 weeks. Similarly, Dupuis et al failed to show any significant differences in thrombin formation between hypercholesterolemic patients with ACS receiving pravastatin 40 mg/d and those taking placebo, although a significant 40% improvement in brachial hyperemic response, a measure of endothelial function, was observed after 6 weeks of statin therapy. These results might imply that when coagulation is triggered by rupture of an atherosclerotic plaque, the TF-lowering (and thrombin) properties of the HMG-CoA reductase inhibitors are too weak to overcome potent prothrombotic mechanisms; however, well-designed studies on much larger groups of patients with ACS are necessary to clarify this issue.

Because thrombin stimulates a number of atherogenic processes, including cell migration/proliferation, leukocyte trafficking, and inflammation, it is tempting to speculate that statin-induced reduction in thrombin formation might also inhibit atherosclerosis via various indirect mechanisms such as modulation of thrombin signaling mediated by G-protein–coupled protease-activated receptors (PARs). Once activated by cleavage at Arg41, PAR-1 via several signaling pathways, including isoprenylated Rho proteins, results not only in posttranscriptional changes but also in altered transcription of a number of genes. For example, the increased expression of TF by thrombin, as documented by several investigators, might be reduced as a result of statin-induced decrease in thrombin formation, in addition to the inhibition of isoprenylation of signal intermediates involved in the function of PAR-1. Fenton et al have proposed a hypothesis that this PAR-1–related mechanism is of particular importance in the expression of antithrombotic effects of the HMG-CoA reductase inhibitors. However, a role of PAR-1 activation in platelets and vascular cells, along with thrombin signaling and transcriptional networks, in the antithrombotic actions ascribed to statins remains to be established.

Fibrinogen and Fibrin
The fibrinogen molecule, comprising 3 pairs of polypeptide chains, denoted Aα, Bβ, and γ, is a principal substrate for thrombin. Thrombin catalyzes the release of fibrinopeptide A (FPA) and B (FPB) from the amino-termini of the Aα and Bβ chains of fibrinogen, respectively, to form fibrin monomer with the resulting structure (α, β, γ), that can polymerize via noncovalent interactions between the D domains and the central E domains of fibrin monomers, resulting in double-stranded fibrils that associate laterally, forming thick fibers. Because elevated fibrinogen levels represent a recognized risk factor for CAD and thrombosis and significantly affect plasma thrombogenicity, the effects of statins on fibrinogen concentrations have been studied extensively. It has been reported that these agents increase, or, in a majority of reports, have no effect on plasma fibrinogen levels. Most, but not all, of the studies, in which fibrinogen concentrations have been measured using the Clauss method, concluded that inhibition of HMG-CoA reductase did not affect fibrinogen concentrations. These observations strongly suggest that the divergent results in fibrinogen determinations are a result, in part, of the use of different laboratory methods, such as nephelometry or turbidimetry. It should be mentioned that some authors claimed that the only exception among statins in this regard might constitute atorvastatin, which has been shown to increase plasma fibrinogen levels by up to 46% in hypercholesterolemic patients receiving 40 or 80 mg daily. This issue is still unclear, as is a potential mechanism for this differential effect of atorvastatin compared with other drugs of this class.

Fibrinogen cleavage, as evidenced by fibrinopeptide levels, has been found to be decreased in patients treated with simvastatin, which provided additional evidence for reduced thrombin generation. Decreased amounts of FPA and FPB have been demonstrated at the site of hemostatic plug formation in hypercholesterolemic men after a 3-month treatment with simvastatin, without any association with cholesterol reduction. The rate of fibrinogen removal from the bleeding-time blood was also significantly retarded and impaired during simvastatin therapy as compared with the time course of this process before treatment. Lower plasma FPA levels, measured using immunoenzymatic assays, have also been reported in hypercholesterolemic subjects after 3 months of therapy with simvastatin. It is unclear whether other statins can alter the release of FPA from fibrinogen.

Factor V/Va
Thrombin is a predominant activator of FV by the cleavage of 3 peptide bonds at Arg 709, Arg1018, and Arg1545. Therefore, it is not surprising that FV activation is impaired as a result of simvastatin therapy; data on effects of other statins are lacking.

FVa, composed of the 105-kDa heavy chain (residues 1 to 679) and the 74-kDa light chain (residues 1546 to 2196), markedly enhances FXa-mediated prothrombin activation in the surface-bound prothrombinase complex. In 2001 we reported that generation of FVa heavy chain and light chain, the limiting steps in FVa formation in vivo, was not only significantly delayed by 30 to 60 seconds but also reduced by ~30% and 19%, respectively, after simvastatin therapy. The decreased rate of FVa formation was associated with a 26% lower rate of depletion of FV from the blood collected at the site of hemostatic plug formation. The rates of FVa formation were unrelated to simvastatin-induced changes in lipid profiles.

Factor XIIIa
Thrombin cleavage of 37 amino acids from the N-terminus of FXIII results in the formation of activated FXIII that forms γ-glutamyl-ε-lysyl bonds between fibrin molecules. Fibrin cross-linking by FXIIIa increases clot stability and resistance to lysis. In a model of microvascular injury, FXIII activation was decreased by ~20% in patients treated with simvastatin as compared with the situation before therapy. Because thrombin is the major FXIII activator in vivo, this
effect most likely reflects decreased thrombin formation observed during statin administration. Changes in FXIII activation at the site of injury were not related to the cholesterol-lowering action of simvastatin.39

Because decreased thrombin levels affect fibrin clot structure leading to the formation of less tightly cross-linked, more porous and easier lysable clots,54 one might speculate that statin therapy through decreased thrombin generation is associated with altered fibrin architecture.

Inhibition
Thrombin formation is suppressed by several inhibitors, including antithrombin, tissue factor pathway inhibitor, heparin cofactor II, and the protein C pathway, the major anticoagulant system in the microvasculature.10,11 This latter system involves protein C, protein S, and thrombomodulin (TM), the transmembrane glycoprotein expressed on the endothelium, particularly abundant in the microvasculature.58

Protein C Pathway
TM forms a high-affinity complex with thrombin that drastically alters the specificity of this protease such that it loses its procoagulant activity and transforms it into an “anticoagulant” enzyme, activated protein C on the surface of endothelial cells.58,59 However, a soluble TM that is shed from the endothelium is a marker of endothelial damage. The concept of increased TM expression is not supported by all studies; discrepancies exist between statin studies that show either the reduction of soluble TM or increased endothelial expression by TM. Several studies have shown reduced (by 12% to 50%) plasma (soluble) TM levels during 3 months of pravastatin therapy in hypercholesterolemia60 and after a 4-week treatment with fluvastatin in recipients of heart transplants,61 whereas others failed to demonstrate any significant statin-induced changes in TM levels.62 These findings led indirectly to the conclusion that statins do not influence or unfavorably affect TM expression, which is essential for effective activation of protein C. In 2003, Masamura et al63 provided compelling evidence that TM expression on endothelial cells significantly increases as a result of statin administration. An inhibition of Rho protein, Rac/Cdc42, was reported to account for a concentration-dependent increase in TM antigen levels by statins, and this effect could be reversed with mevalonate or geranylgeranyl pyrophosphate.63 Furthermore, it has been demonstrated recently that upregulation of TM expression in human endothelium after statin therapy is mediated via a NO-dependent mechanism.64

Membrane-bound FVa is inactivated by activated protein C (APC) through cleavages of the heavy chain at Arg506, Arg306, and Arg679.65 Loss of the cofactor activity is associated with cleavages at Arg506 and Arg306 with a reduction of soluble TM or increased endothelial expression during statin therapy.58

Of the protein C anticoagulant system, inhibit the coagulation cascade, and, consequently, contribute to the antithrombotic potential of these agents observed in vivo.

The 97-kDa fragment of FVa heavy chain, a probable product of FVa proteolysis at Arg643 by thrombin in the presence of endothelial cells and/or platelets is another indicator of FVa inactivation.56,67 This product is observed within the last 1 to 2 minutes before the end of bleeding. By immunoblotting, we have demonstrated that at the site of microvascular injury simvastatin is able to enhance the generation of this fragment independently of cholesterol lowering,39 which suggests a more efficient inactivation of FVa, independent of the APC activity, because of statin administration. Potentially, alternative cleavage products are favored for FVa inactivation on the vasculature when the anticoagulant effects of statins are present. The role of this alternative inactivation pathway of factor Va and cleavage in the overall scheme of factor Va metabolism and statin therapy requires further elucidation.

Tissue Factor Pathway Inhibitor
Tissue factor pathway inhibitor (TFPI) is the only physiological inhibitor of the TF–FVIIa complex that also neutralizes the catalytic activity of FXa.68 Because 80% of TFPI is bound to LDL, drug-induced changes in lipid profile have been suggested to affect the activity of this inhibitor. However, conflicting results have been reported.3,5,8 Lovastatin,69 fluvastatin,70 simvastatin,71 and atorvastatin36 have been found to decrease TFPI activity, caused by reduction in the LDL–TFPI complexes, and total TFPI levels without any change in free TFPI in hyperlipidemic individuals. The reported lower TFPI antigen levels as a result of the HMG-CoA reductase inhibitors are likely to reflect normalization of the disturbed functions of the endothelium, but not suppression of the anticoagulant potency of the endothelial pool of free TFPI, mobilized by heparin, as shown by Hansen et al.69 The available data indicate a lack of significant changes in TFPI levels and/or activity during statin therapy.

Other Effects
There is evidence that statins may modulate FVIII activity.8 Simvastatin (10 to 40 mg/d) has been found to decrease FVIII activity, usually in conjunction with reduced levels of the carrier protein, von Willebrand factor.71 However, most studies have yielded data showing no effect of statins on this variable and FVIII levels.34,54,61 Methodological problems with specific assays for determination of FVIII activity in blood samples might explain divergent results. The actual impact of inhibition of the HMG-CoA reductase inhibitors on FVIII requires further studies.

Clinical Implications
Rapidly accumulating evidence for statin-induced suppression of blood coagulation in vivo suggests that statin therapy may be useful in treating vascular disorders with a strong thrombotic component, such as the acute thrombotic complications of atherosclerosis. From the epidemiological point of view, a role of statins in the management of ACS would be of utmost significance. In the MIRACL (Myocardial Ischemia
Reduction with Aggressive Cholesterol Lowering) study,72 an early initiation of high-dose statin therapy (atorvastatin 80 mg/d) within the first 24 to 96 hours after hospital admission for ACS has been associated with a 52% LDL cholesterol-lowering and 16% lower relative risk for a primary composite end point (death, nonfatal myocardial infarction, recurrent angina) at 16 weeks (14.8% versus 17.4%). In recent years, retrospective analyses of large randomized double-blind statin trials and registry data, for example, the Swedish Registry of Cardiac Intensive Care77 of 20 000 patients with the first myocardial infarction from 1995 to 1998, strongly supported the early use of statins in subjects with ACS.74 The ongoing trial, Pravastatin in Acute Coronary Syndromes Trial, will help define benefits of statin use in patients with ACS.

Considering that a majority of the known anticoagulant effects of the HMG-CoA reductase inhibitors are independent of cholesterol lowering, it is not surprising that the beneficial effects of these drugs have been reported in patients with not only elevated but also normal LDL cholesterol levels. The most compelling evidence for this view stems from the Heart Protection Study (HPS) evaluating the effects of simvastatin 40 mg/d versus placebo in >20 000 high-risk patients, aged 40 to 80 years, treated for an average of 5.5 years.75 A significant reduction in risk for vascular events did not depend on the baseline LDL cholesterol level; the patients with the level of <2.6 mmol/L (100 mg/dL) had the same 24% lower risk for CAD or stroke as that observed for the entire study population.75 Nevertheless, no consistent evidence available has shown beyond reasonable doubt that the antithrombotic effects of statins do significantly contribute to marked benefits reported in recent and older statin trials.

Based on numerous reports showing that the HMG-CoA reductase inhibitors can reduce thrombin generation,29–31,35–39 one might suspect that their use might protect to some extent against venous thrombosis. In addition, there is some evidence for an association between hypercholesterolemia, either with or without triglyceridemia, and objectively documented deep vein thrombosis.76 Until now, the strongest evidence supporting the presence of links between lower risk for thromboembolism and statin administration has come from a post-trial analysis of results of the Heart and Estrogen/progestin Replacement Therapy Study (HERS)77 and a retrospective Canadian cohort study.78 In the first study, statins, but not other lipid-lowering agents, reduced the risk of venous thromboembolism by 50% in postmenopausal women,77 whereas in the second, >125 000 men and women, aged 65 years and older, treated with these drugs had a 22% lower risk for deep vein thrombosis.78 Very recently, Doggen et al79 reported that in postmenopausal women, simvastatin, but not pravastatin, decreases the adjusted risk of venous thromboembolism by 50% and higher doses of simvastatin tend to be more effective than those <40 mg daily. To date, only one study, a population-based retrospective follow-up with a nested case control analysis performed in the UK among patients without CAD or other atherosclerotic vascular diseases,80 has not shown a protective effect of statins against venous thrombosis. However, there are no data from randomized clinical trials regarding a potential role of HMG-CoA reductase inhibitors, in combination with anticoagulants or not, in the prevention of thromboembolism. Undoubtedly, given increasing incidence of this disease in Western countries and widespread use of statins, elucidation of this intriguing issue could be of importance for clinical practice.

Conclusions

Statins are the most powerful cholesterol-lowering drugs available. Although a major beneficial effect of statins in clinical studies is related to a marked reduction in LDL cholesterol levels, there is good evidence that among multiple vascular protective effects, HMG-CoA reductase inhibitors can also exhibit antithrombotic properties that, in most cases, are not associated with changes in lipid profile (Table). These effects, involving decreased TF expression and reduced thrombin generation and attenuation of several pro-coagulant reactions catalyzed by thrombin, such as fibrinogen cleavage, FV and FXIII activation, coupled to increased thrombomodulin expression, are mostly attributed to inhibition of isoprenylation of signaling proteins, a covalent modification essential for their interaction with cell membranes. However, it is still unclear to what extent these properties predominantly observed in vitro and/or animal models contribute to reductions in cardiovascular morbidity and mortality associated with the use of the HMG-CoA reductase inhibitors. Moreover, whether all statins available share similar mechanisms of anticoagulant properties remains uncertain. Future basic research and clinical studies will help to understand an actual impact of the HMG-CoA reductase inhibitors on complex series of reactions of the blood coagulation cascade and, importantly, to establish a role of these drugs in the prevention and treatment of arterial thrombosis in the atherosclerotic vessels and possibly also that of venous thrombosis.

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